## REMARKS

Claims 1, 4-16, 29-38, 40-48, 55 and 56 are pending in the application. Claims 2, 17-28, 49-54, 57 and 58 have been canceled.

Claims 1, 7, 12, 14, 44, 48 and 55 have been amended. In the specification, the first full paragraph on page 5, the last paragraph on page 11 and continuing onto page 12, the third full paragraph on page 15, and the last paragraph on page 18 and continuing onto page 19 have been amended. No new matter has been added.

Because the present amendments (1) do not raise new issues requiring further consideration or search, (2) do not introduce new matter, (3) materially reduce the issues for appeal, and (4) place this application into better condition for allowance, entry is appropriate under 37 C.F.R. § 1.116, and is respectfully requested.

Based on the following remarks, Applicant respectfully requests reconsideration and allowance of the pending claims.

Objection to the Previous Amendment

The Examiner has objected to the amendment filed April 21, 2003 because claim 7 on page 11, under the heading "PENDING CLAIMS" differs from claim 7 as originally filed, but claim 7 has not been amended. The Examiner is correct that Applicant intended to amend claim 7 in the previously filed amendment. Applicant respectfully submits that claim 7 has now been amended as suggested by the Examiner in the Office Action mailed October 21, 2002 and in the format required by 37 C.F.R. 1.121.

Objection to the Specification

The Examiner has objected to the specification because of the use of improperly demarcated trademarks. It is Applicant's understanding that a corporation name does not require the use of a symbol such as ™ or ®. However, Applicant has amended the specification as suggested by the Examiner and respectfully submits that the amendments to the specification overcome the Examiner's objection.

Claim Objections

Claim 14, 44 and 48 have been objected to on the basis that a peptide is not encoded by amino acid residues, but rather by polynucleotide residues. Applicant respectfully submits that the amendments to claims 14, 44 and 48 filed herewith overcome the Examiner's objection.

Claim 44 has been further objected to because of a typographical error listing SEQ ID NO: 1 instead of SEQ ID NO: 2. Applicant has amended the claim as suggested by the Examiner and respectfully requests reconsideration thereof.

Claim Rejections under 35 U.S.C. § 112

*1. Enablement*

The Examiner has rejected claims 1 and 4-16 under 35 U.S.C. § 112, first paragraph. The Examiner states that the specification, while being reasonably enabling for a method for preventing melanoma in mice immunized with HP59/CFA does not reasonably provide enablement for a method for preventing cancer in a mammal.

The Examiner has rejected claims 30-38 and 40-48 under 35 U.S.C. § 112, first paragraph. The Examiner states that the specification, while being reasonably enabling for a

composition consisting of a mixture of Hab1, Hab2 and Hab3, or alternatively consisting of a mixture of p55a, p56a, p57a, Hab1 and Hab2 for attenuating tumor burden in mice challenged with melanoma or Lewis lung tumor cells and reasonably enabling for a method for protecting against melanoma in mice immunized with HP59/CFA, does not reasonably provide enablement for a composition for protecting against or attenuating cancer.

The Examiner has rejected claims 55 and 56 under 35 U.S.C. § 112, first paragraph. The Examiner states that the specification, while being enabling for a method for producing a composition consisting of a mixture of Hab1, Hab2 and Hab3, or alternatively consisting of a mixture of p55a, p56a, p57a, Hab1 and Hab2 for attenuating tumor burden in mice challenged with melanoma or Lewis lung tumor cells and reasonably enabling for a method for producing a composition consisting of HP59/CFA for protecting against development of melanoma in mice, does not reasonably provide enablement for a method for producing a composition for treatment and/or prevention of cancer.

Applicant respectfully traverses these rejections and requests reconsideration and withdrawal thereof.

The Examiner points to the articles cited by him in the previous Office Action and the Espinoza-Delgado reference cited by Applicant for the proposition that clinical responses in humans have not been achieved through the induction of antitumor T cell activity. The Examiner cited a general statement from Yu et al. (*J. Clin. Inv.* 110: 289-294, Aug. 2002) to the effect that "we do not have a cancer vaccine in hand that can reliably increase patient survival or induce tumor destruction." Applicant respectfully submits that this statement

says nothing as to whether Applicant's claims are enabled and in fact, supports the novelty and nonobviousness of Applicant's invention.

Applicant respectfully submits that the *Yu et al.* reference actually teaches that one skilled in the art can extrapolate experimental data from mice to reliably predict the outcome of treatments in mammals, including humans. In the section of the paper discussing "future directions," *Yu et al.* encouragingly states that many new transgenic mouse models are now available that can be used for the development of cancer vaccines. Therefore, *Yu et al.* clearly promotes the fact that a successful result in animal research can be extrapolated to humans. *See Yu et al.*, at page 293, second column, second full paragraph. As further evidence that a person with skill in the art routinely extrapolates experimental data from mice to predict the outcome of treatments in mammals, including humans, Applicant submits Attachment A, Allen Bradley, "Mining the Mouse Genome," *Nature* 420, 512-514 (Dec. 5, 2002), which states:

> **Over the past two decades, the mouse has emerged as the pre-eminent model organism for two fundamental reasons.** First, it is a mammal, and so has many physiological, anatomical and metabolic parallels with humans. Although the anatomical differences between humans and mice appear striking, they reflect alterations in size and shape — detailed analysis of organs, tissues and cells reveals many similarities, extending to whole-organ systems, physiological homeostasis, reproduction, behaviour and disease. **The mouse is an excellent surrogate for exploring human biology, and disease processes in the animal can accurately reflect those in humans. This explains why the mouse is widely used to investigate diverse aspects of mammalian biology and pathology, ranging from embryonic development to metabolic disease, behaviour and cancer in adults.**

Furthermore, Applicant respectfully submits that the Examiner's position is contrary to controlling caselaw which states that human testing is not required to obtain a patent. The

United States Court of Appeals for the Federal Circuit has held that Title 35 does not demand that human testing occur within the confines of the Patent and Trademark Office proceedings. *See Scott v. Finney,* 34 F.3d 1058, 1063, 32 U.S.P.Q.2d 1115 (Fed. Cir. 1994). A copy of this case can be found at Attachment B for the Examiner's convenience.

*2. Written Description*

Claims 55 and 56 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner notes that Applicant intended to amend claim 55 in the amendment filed April 21, 2003 to obviate this ground of rejection. Applicant respectfully submits that the current amendment to claim 55 overcomes this rejection.

*3. Definiteness*

Claim 7 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner notes that Applicant intended to amend claim 7 in the amendment filed April 21, 2003 to obviate this ground of rejection. Applicant respectfully submits that the current amendment to claim 7 overcomes this rejection.

Claim Rejections under 35 U.S.C. § 102

The Examiner has rejected Claims 4, 6, 7, 15, 16, 55 and 56 under 35 U.S.C. § 102(b) as being anticipated by Nair et al. (*Int'l J. Cancer* 70: 706-715, 1997).

To anticipate a claim, a reference must teach each and every element of the claim, either expressly or inherently. *See* M.P.E.P. § 2131. *Nair et al.* fails to teach administering an amount of at least one GBS toxin receptors or immunogenic fragments thereof having

substantial identity to SEQ ID NO: 2 effective to induce or maintain an immune response to at least one of the GBS toxin receptors. *Nair et al.* teaches a method to generate an immune response to tumors by immunizing a mouse with dendritic cells which have been loaded with tumor extract containing a mixture of tumor antigens. Applicant respectfully submits that *Nair et al.* purposely uses unfractionated extracts from poorly immunogenic tumors to demonstrate the adjuvant effect of the dendritic cells, which present antigen to the T cells.

At page 9 of the Office action, the Examiner states that "absent a showing of any difference, the composition of the prior art, which is administered to the mammal, is deemed to comprise an amount of a GBS toxin receptor having substantial identity to SEQ ID NO: 2, which is effective to induce or maintain an immune response to HP59." Applicant takes this to mean that the Examiner believes that *Nair et al.* inherently teaches this element of the claims. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency of that thing. *See* M.P.E.P. § 2112. In relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teaching of the applied prior art. *Id.* Applicant respectfully submits that the Examiner has failed to provide a basis to support his statement that the composition of *Nair et al.* includes an amount of a GBS toxin receptor having substantial identity to SEQ ID NO: 2 which is effective to induce or maintain an immune response to HP59.

Applicant respectfully submits that the GBS toxin receptor is found on the vasculature supporting the growth of tumors, not the tumors themselves. As described in the

specification on page 5, lines 20-32, the GBS toxin receptor is present on the pathological neovasculature feeding a tumor. The receptor is expressed in medical conditions involving pathologic angiogenesis. The claimed method and composition prevent the pathologic condition by causing an immune response that attacks abnormal blood vessels such as those that provide nutrients to a growing tumor. In contrast, *Nair et al.* administers tumor extracts from the MBT-2 cell line, derived from a bladder tumor, and tumor extracts from the F10.9/K1 cell line, derived from a melanoma. Applicant submits that administration of tumor extracts from a cell line would not include administration of blood vessels and thus, would not include administration of the GBS toxin receptor. Applicant respectfully traverses this rejection and requests reconsideration and withdrawal thereof.

## CONCLUSION

In light of the amendments and the above remarks, Applicants are of the opinion that the Office Action has been completely responded to and that the application is now in condition for allowance. Such action is respectfully requested.

If the Examiner believes any informalities remain in the application that may be corrected by Examiner's Amendment, or there are any other issues that can be resolved by telephone interview, a telephone call to the undersigned attorney at (404) 815-6409 is respectfully solicited.

Respectfully submitted,

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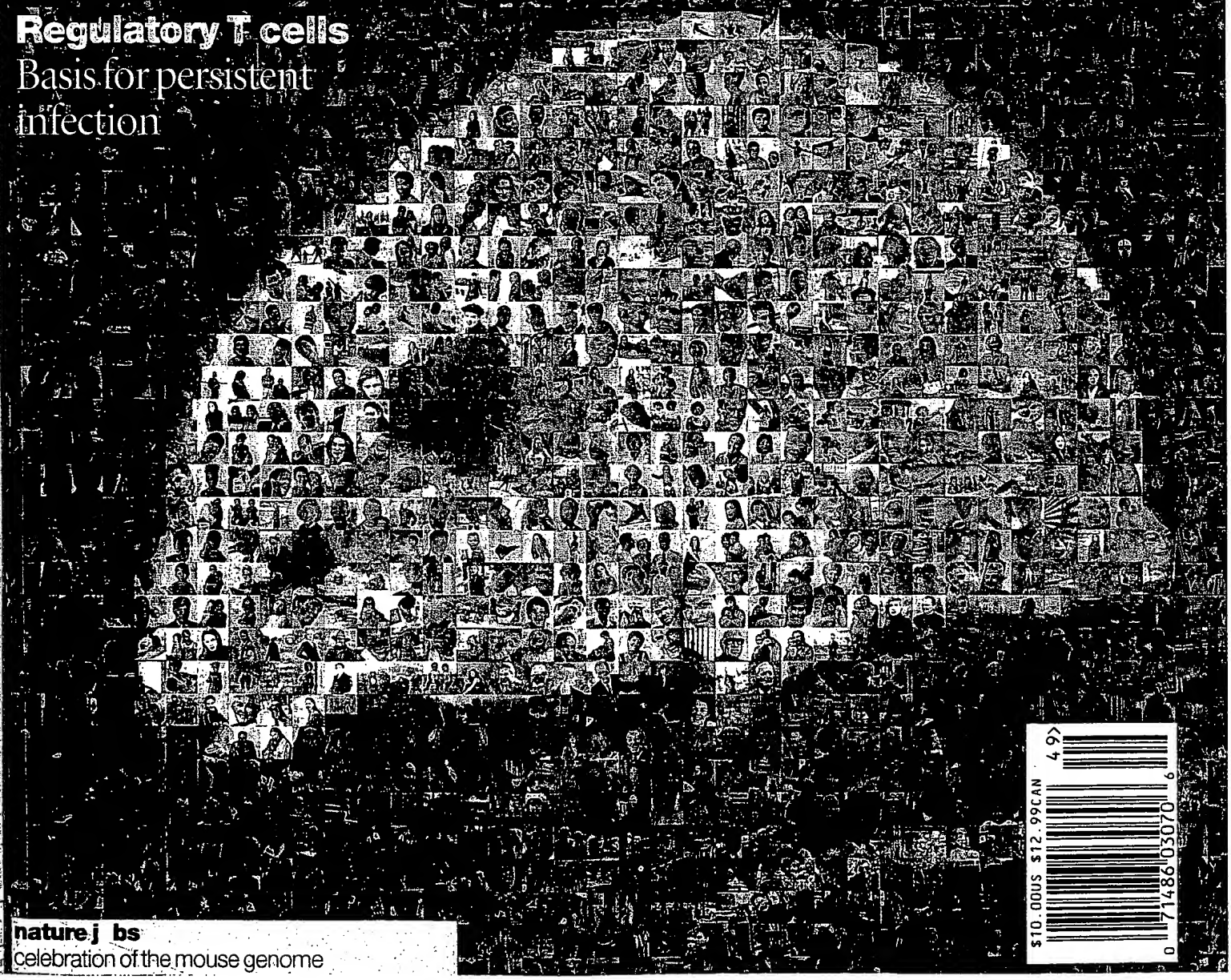
## The mouse genome

Experimental model for human biology



nature.j bs
celebration of the mouse genome

# Mining the mouse genome

## We have the draft sequence — but how do we unlock its secrets?

**Allan Bradley**

The mouse genome sequence, published in this issue[1], has already made a huge impact on the research community. Although only a draft, it is clear that the sequence is a very high-quality product, with excellent coverage and reliability over large genomic expanses. It is a huge asset to researchers, and its significance matches that of the human genome. In the past six months, for example, the Ensembl genome browser of the Sanger/European Bioinformatics Institute dealt with 2.6 million requests for detailed information about the mouse genome, and 3.2 million queries about the human sequence.

But there is one important difference between these two resources — the mouse genome encodes an experimentally tractable organism. This means that it is now truly possible to determine the function of each and every component gene by experimental manipulation and evaluation, in the context of the whole organism.

### An ideal tool

Over the past two decades, the mouse has emerged as the pre-eminent model organism for two fundamental reasons. First, it is a mammal, and so has many physiological, anatomical and metabolic parallels with humans. Although the anatomical differences between humans and mice appear striking, they reflect alterations in size and shape — detailed analysis of organs, tissues and cells reveals many similarities, extending to whole-organ systems, physiological homeostasis, reproduction, behaviour and disease. The mouse is an excellent surrogate for exploring human biology, and disease processes in the animal can accurately reflect those in humans. This explains why the mouse is widely used to investigate diverse aspects of mammalian biology and pathology, ranging from embryonic development to metabolic disease, behaviour and cancer in adults.

Second, although it is certainly true that mammalian biology is available in other species that in some cases are closer to humans, the mouse has one feature that has been uniquely developed compared with all other mammals — genetic tractability. The similarities in biology and pathology between mouse and human are reflected in the genomes. For virtually every gene in the human genome, a counterpart can readily be identified in the mouse. Genetic manipulation within the living mouse is routine and can these days be done with extraordinary precision. Consequently, many mouse strains have been generated with genetic lesions that echo those observed in human genetic disease.

In some cases, these manipulations yield a model that closely resembles the pathology of the analogous human condition — for example, the susceptibility to cancer of mice deficient in the gene encoding the protein p53 resembles that of humans who have mutations of their p53 gene. In other cases, only some aspects of the human pathology are apparent; for instance, mice with mutations in the cystic fibrosis gene do not develop lung disease, which is the most devastating aspect of the condition in humans. Understanding how the disease process is suppressed in mice will provide important clues for treating the human condition. Genetic studies in mice are greatly helped by the availability of inbred strains, which allow experimental parameters to be measured in a homogeneous genetic background.

The mouse genome sequence[1] is already fuelling the next phase of research. At a very fundamental level, we now have a reasonable 'parts list' for the mouse. Some of these parts — the transcription units — are the elements we understand best. Although there are now many new gene transcripts to explore, existing experimental methods can be used to examine them. But the mouse genome also contains many non-coding regions of sequence identical to their counterparts in the human genome. New experimental methods will have to be deployed to examine the function of these conserved sequences.

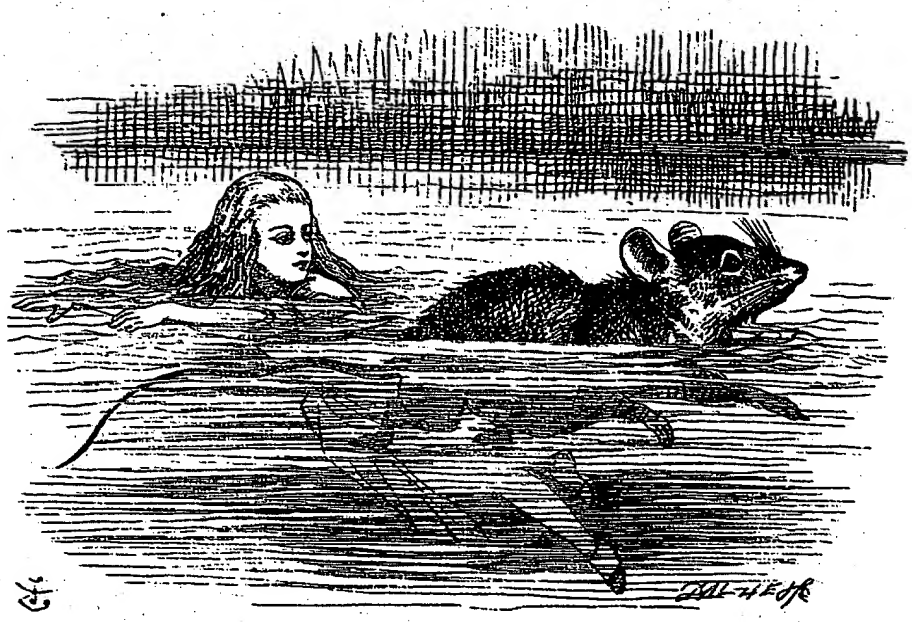
The complementary DNA (cDNA) clone and sequence resource described on page 563 by a group from the Institute of Physical and Chemical Research (RIKEN) in Japan[2], illustrates the potential usefulness of the mouse genome sequence. The authors' comparison of their FANTOM clones with the genome sequence immediately illustrates gene structures that will enable the mutagenesis work discussed below. The physical cDNA resource can be used in many experimental situations: for instance, in over-expression studies in cell lines or transgenic mice (in which the product of the gene concerned is made in abundance to allow its function to be investigated); to produce proteins for structural studies or antigens to obtain antibodies for investigating gene expression; or in studies of interactions between different proteins. For laboratories interested in a single cDNA clone, knowledge of the end-points of the messenger RNA is sufficient to design primers to rapidly retrieve a cDNA by reverse-transcriptase PCR (polymerase chain reaction) analysis, saving months of time 'walking' through cDNA libraries. The mouse cDNA parts list is already being used to illuminate patterns of gene expression.

Although the draft mouse genome sequence is available now, it will be two years before it is a finished, reference-quality product. Even so, the annotation of function to genes is already under way on a small scale in many laboratories, and larger-scale studies are being initiated. Unlike DNA sequencing, experimental work is not always amenable to high-throughput, automated approaches and can be complex to interpret. The research community clearly faces an enormous task — one that will extend well beyond the next decade.

### Joined-up efforts

The assembled mouse genome provides a framework onto which functional information will increasingly be layered. Genome browsers (see Box, overleaf) provide an interactive graphical view of the genome, rendering its vast size (equivalent to a million pages of text) accessible to the scientific community. They can provide detailed information about a single gene, or enable a wider perspective of the genomic landscape in a single species or across several species.

Mutation data, phenotype information and gene-expression data (described below) are just three of the many potential data sets that have to become accessible by these means. Many laboratories generating large data sets with 'post-sequence' goals in mind recognize the need to make their data accessible electronically. But few have sought ways to link their data back to a browser, and many may not have



**Pooled resources: the mouse sequence will offer insight into the workings of the human genome.**

access to the computational infrastructure needed to respond to a large volume of queries. The mouse genetics community has enjoyed an exceptionally high-quality mouse genome database for many years (see Box, overleaf), but this must continue to evolve and be intimately integrated with genome browsers. Joined-up data sets are essential if we are to reap the potential rewards from the mouse genome.

The draft mouse genome is being intensively scrutinized, but how much functional information can be deciphered from sequence-gazing alone? Which experimental approaches will provide the greatest information for the resources spent? Computational prediction and alignment programs can already identify many genes and predict some aspects of gene structure. Yet computers remain inferior to cellular machinery in recognizing a gene, where it starts and stops, and when it should be turned off and on. At best, computer predictions provide a very incomplete picture of a genome. Detailed 'hand-crafted' curation, coupled with experimental analysis, is necessary to clarify the encoded gene set. The paper from RIKEN[2] goes some way towards satisfying the need to identify the complete set of mouse genes. This resource must be distributed widely and quickly, without restrictions on access or usage, if the value of the clone set is to be realized.

## Untangling the genome

Computational analysis is also being used to classify genes into families based on conserved motifs in the gene sequences, although such functional insights are limited to some classification of a protein's biochemical activity or cellular function based on the motifs. For instance, transcription factors and enzymes can be recognized from their motifs, but not where and when they would be expressed and who their partners are. This information is encoded in the genome, but it is indecipherable at present and so impossible to extrapolate to the physiological role of any gene.

> Joined-up data sets are essential if we are to reap the potential rewards from the mouse genome.

Considerably more experimental information is needed to predict gene function, but which experimental approaches are applicable to high-throughput analysis of large gene sets in complex multicellular organisms? Several groups believe that information on gene expression is invaluable and should be generated for every gene in the genome. The expression pattern of a gene in a multicellular organism is a basic feature of the biological function of any gene, whatever its function. The more contexts in which expression is examined, the greater the insight into function. In principle, a definitive and comprehensive atlas of the expression pattern of every gene in the genome can be generated.

One experimental approach in which thousands of genes can be analysed in parallel is to isolate messenger RNA and to display the gene-expression profile on a chip. When this technique is applied to tissues, data are lost because aspects of the three-dimensional structures of multiple cell types are destroyed in the biochemical extraction. Data from *in situ* analyses contain more detailed information about each gene, but the generation of these data is serial and significantly slower.

Gene expression is being systematically examined at the transcriptional level by several groups, for instance in the 9.5-day-old mouse embryo and in adult tissues (see Box, overleaf). Two other papers in this issue[3,4] report large-scale analyses of gene expression in embryonic and adult stages, but so far have examined just 0.5% of the genes in the genome, the homologues of the genes on chromosome 21. Transcription studies *in situ* have relatively limited resolution, and the tissues constituting a multicellular organism are complex mixtures of different cell types. Unless each cell is individually visualized for gene expression in combination with histological criteria, important information relating to biological function is lost, for instance the subcellular compartment(s) occupied by a protein.

The Sanger Institute's Atlas project is being established to systematically examine the expression pattern of every gene product at tissue-, cellular- and subcellular-level resolution, to provide a permanent, definitive and accessible record of the molecular architecture of normal tissues and cells. The ultimate goal is to define protein expression patterns for all 30,000 mouse genes in hundreds of different tissues, all gathered in archival data sets to support research projects worldwide. Data will be collected electronically and archived with a vocabulary allowing complex queries.

A protein's location in a cell and a tissue provides important clues about its function, but such data are still insufficient to reveal its physiological role *in vivo*, or the temporal and spatial specificity of gene products for an as-yet-unknown functional activity. Gene-expression data are informative and can guide an experimental path, but cannot be interpreted in isolation.

## Mutational analysis

One of the most informative experimental approaches for examining gene function is to analyse mutants. Spontaneous and induced mutations in the mouse have been studied for more than 100 years, but in the past decade there has been an explosion in their use.

The isolation of embryonic stem (ES) cells[5] and demonstration that these cultured cells can recolonize the mouse germ line[6] were the two fundamental discoveries that led to the first 'knockout' mouse in 1987, through a genetic modification that had been engineered *in vitro*. This heralded a golden era for mouse genetics. Today, it is possible to engineer mice with genetic changes as subtle as a single nucleotide substitution or with major alterations of the genome such as the deletion or duplication of millions of base pairs[7]. The genetic tractability of ES cells has made the mouse uniquely accessible for genetic studies compared with every other multicellular organism.

Despite this success, the combined output of the mouse genetics community over

the past 10 years has described mutations in just a few thousand genes by this method, 10–15% of the predicted gene content of the organism. Can this rate be speeded up so that it will not take 50 years to mutate and analyse the remaining 85–90%? Several leading mouse genetics laboratories have begun to discuss plans to generate a knockout for every gene in the mouse genome, but how will this be achieved?

Gene targeting requires detailed knowledge of gene structure to ensure that the target locus has been effectively mutated. One of the most immediate practical benefits of the assembled mouse genome sequence is the availability of detailed gene-structure information, enabling mutations to be made with a full understanding of the likely functional consequences. Knowledge of the genome sequence has also made it possible to index libraries of gene-targeting vectors, eliminating the need to screen a library to obtain a genomic clone for targeting. Library indexing by end-sequencing significantly increases the rate at which knockout mice can be generated.

## On target

Although the genome sequence has enhanced the rate at which targeted mutations can be generated, is this going to be fast enough? Targeting is an inherently serial process — a single experiment typically generates one type of allele. Gene trapping, on the other hand, in which genes are tagged for sequence retrieval by insertional mutagenesis, generates hundreds of different mutations from a single electroporation or viral infection. Recognizing the importance of a genome-wide gene-trap library, but unable to fund this in the academic sector, I and other colleagues set up Lexicon Genetics. Although the Lexicon resource is now quite comprehensive, the cost is significant, intellectual property rights may have to be negotiated, and some mutants will not be available for commercial reasons.

There are also gene-trap libraries in the public sector (see Box), through which about 16,000 ES cell clones are now available. In principle, these resources should be distributed with few constraints. Although their coverage is more limited and the effort less centralized than the Lexicon library, over the next couple of years this resource should expand considerably. The value of such an archive will be fully realized only if it can be exploited by the community. One key aspect of the elaboration of this resource is to ensure that the knowledge of the location of these mutations in the genome is linked with access to the physical resource (the trapped ES cell clone), so that ES cell clones can be retrieved and used to establish mice carrying these mutations.

Over the past decade, knocking out genes has provided a rich source of information about gene function — and as a result, this sequence-driven approach has been widely adopted. But there is considerable uncertainty in predicting the phenotypes that will be displayed by the mutant mice. In my own view, selection of a candidate gene for mutational analysis might as well be stochastic as based on assimilation of existing knowledge.

Sadly, our knowledge of conserved domains, expression patterns, biochemical activity, protein–protein interactions and molecular structure is inadequate to predict function. A knockout phenotype often shamelessly displays our collective ignorance about gene function. We have to accept that in many cases, sequence-directed mutagenesis may not efficiently identify genes specific to certain functions or disease — for instance, the genes involved in diabetes — by knocking out individual candidates.

Mutational analysis can be focused to identify the players in a specific process by performing a genetic screen, as widely used in organisms such as the yeast *Saccharomyces cerevisiae*, the nematode worm *Caenorhabditis elegans*, and the fruitfly *Drosophila melanogaster*. Screens did not catch the imagination of the mouse community when first introduced 15 years ago because they emerged in parallel with gene-targeting approaches, which looked so promising. Over the past few years, genetic screens have become much more popular because of a few high-profile successes[8]. Currently, ENU (*N*-ethyl-*N*-nitrosourea) mutagenesis is the most widely used method for random mutagenesis, and several programmes using this approach have been initiated (see Box).

Although the 1,000-plus new mutations generated by ENU mutagenesis provide a resource for future studies, they will not add any knowledge about gene function until the underlying genetic lesions have been identified, and the molecular mechanisms relating the lesion to the observed phenotype are understood in detail. This leaves the strategy with two major bottlenecks — the identification of the mutation (typically a nucleotide substitution); and a detailed phenotypic understanding of each mutant.

## Community work

Whatever method is used to generate a mutation, understanding the mechanistic cause of the observed phenotype is central to determining gene function. This understanding depends not only on knowing the mutated gene, but also on having a very detailed picture of the phenotype. Several centres are developing standardized expertise in this area, but high-throughput screens will not detect subtle variations from normal, nor will they examine mice for every possible phenotype. Some of the most valuable screens will be pursued in the context of very detailed phenotyping, possibly in the context of another genetic alteration in the background of the mice being screened.

So the job of phenotyping mutants for a specific characteristic is a task that cannot be easily delegated to a centre; rather, it is an activity for the whole community. This requires the mobility of existing strains between groups and availability of funding to pursue smaller, more scientifically focused, screens in specific areas of biological expertise. Progress in understanding the mouse genome will involve the input of diverse experimental approaches in thousands of small and a few large laboratories. The accessibility of mutants is key to this progress, and this comes with a cost — because strains will need to be maintained or archived for decades. So the avalanche of genome sequence will be followed by an explosion of mutant mice, requiring new mouse facilities to house and phenotypically evaluate this global genetic resource. ■

*Allan Bradley is at the Wellcome Trust Sanger Institute, Hinxton, Cambridge CB10 1SA, UK.*

**Web links**

Genome browsers
- **www.ensembl.org**
- **www.ncbi.nlm.gov/genome/guide/mouse**
- **genome.ucsc.edu**

Expression information
- **genex.hgu.mrc.ac.uk**
- **bodymap.ims.u-tokyo.ac.jp**
- **tigem.it**
- **chr21.molgen.mpg.de/data**

ENU mutagenesis centres
- **www.mouse-genome.bcm.tmc.edu**
- **www.mgu.har.mrc.ac.uk/mutabase**
- **pga.jax.org**
- **www.jax.org/nmf**
- **www.gsf.de/leg/groups/enu-mouse.html**
- **jcsmr.anu.edu.au/group_pages/mgc/MedGenCen.html**
- **cmhd.mshri.on.ca**
- **tnmouse.org**

Gene-trap consortium sites
- **www.genetrap.de**
- **www.escells.ca**
- **baygenomics.ucsf.edu**
- **www.lexgen.com**

Mouse genome database
- **www.informatics.jax.org**

1. Mouse Genome Sequencing Consortium *Nature* 420, 520–562 (2002).
2. The FANTOM Consortium and the RIKEN Genome Exploration Research Group Phase I & II Team *Nature* 420, 563–573 (2002).
3. Reymond, A. *et al. Nature* 420, 582–586 (2002).
4. The HSA21 Expression Map Initiative *Nature* 420, 586–590 (2002).
5. Evans, M. J. & Kaufman, M. H. *Nature* 292, 154–156 (1981).
6. Bradley, A., Evans, M. J., Kaufman, M. H. & Robertson, E. J. *Nature* 309, 255–256 (1984).
7. Ramirez-Solis, R., Liu, P. & Bradley, A. *Nature* 378, 720–724 (1995).
8. Vitaterna, M. H. *et al. Science* 264, 719–725 (1994).

▷

United States Court of Appeals,
Federal Circuit.

F. Brantley SCOTT and John H. Burton, Appellants,
v.
Roy P. FINNEY, Appellee.

**No. 94-1090.**

Sept. 14, 1994.

In interference proceeding involving self-contained penile implant invention, the Board of Patent Appeals and Interferences, interference No. 102,429, awarded priority to senior party on grounds that junior party failed to show reduction to practice before senior party's date of invention. Junior party appealed. The Court of Appeals, Rader, Circuit Judge, held that junior party sufficiently demonstrated reduction to practice through videotape of insertion of prototype into penis of anesthetized patient, which showed surgeon manipulating implanted device several times to successfully simulate erection.

Reversed and remanded.

West Headnotes

[1] **Patents** 314(5)
291k314(5) Most Cited Cases

[1] **Patents** 324.5
291k324.5 Most Cited Cases

Issue of reduction to practice of invention is question of law which Court of Appeals reviews de novo.

[2] **Patents** 113(1)
291k113(1) Most Cited Cases

Court of Appeals reviews Board of Patent Appeals and Interference's factual findings under clearly erroneous standard.

[3] **Patents** 90(5)
291k90(5) Most Cited Cases

To show prior invention, junior party must show reduction to practice of invention before senior party, or, if junior party reduced to practice later, conception before senior party followed by reasonable diligence in reducing it to practice; to show reduction to practice, junior party must demonstrate that invention is suitable for its intended purpose.

[4] **Patents** 90(5)
291k90(5) Most Cited Cases

When testing is necessary to show proof of actual reduction to practice of invention, embodiment relied upon as evidence of priority must actually work for its intended purpose.

[5] **Patents** 90(5)
291k90(5) Most Cited Cases

In cases requiring testing in order to show reduction to practice of invention, testing requirement depends on particular facts of each case, with court guided by commonsense approach in weighing sufficiency of testing.

[6] **Patents** 90(5)
291k90(5) Most Cited Cases

Reduction to practice of invention does not require that invention, when tested, be in commercially satisfactory stage of development; testing need not show utility beyond a possibility of failure, but only utility beyond probability of failure.

[7] **Patents** 324.55(1)
291k324.55(1) Most Cited Cases

In interference proceeding, when reviewing sufficiency of evidence of reduction to practice, Court of Appeals applies reasonableness standard.

[8] **Patents** 90(5)
291k90(5) Most Cited Cases

Character of testing necessary to show reduction to practice varies with character of invention and problem it solves.

[9] **Patents** 106(3)
291k106(3) Most Cited Cases

In interference proceeding involving self-contained penile implant unit permitting simulation of erection, junior party sufficiently demonstrated reduction to practice through videotape of insertion of prototype into penis of anesthetized patient, which showed surgeon manipulating implanted device several times

to successfully simulate erection; showing of reduction to practice did not require human testing in actual use circumstances during intercourse.

**Patents 328(2)**
291k328(2) Most Cited Cases

4,791,917. Cited.

***1059** Rudolph E. Hutz, Connolly, Bove, Lodge & Hutz, Wilmington, DE, argued, for appellants. With him on the brief was Harold Pezzner.

Thad F. Kryshak, Quarles & Brady, Milwaukee, WI, argued, for appellee. With him on the brief was Thomas W. Ehrmann.

Before LOURIE, RADER, and SCHALL, Circuit Judges.

RADER, Circuit Judge.

The Board of Patent Appeals and Interferences awarded priority in Interference No. 102,429 to the senior party, Dr. Roy P. Finney. The Board held that the junior party, Dr. F. Brantley Scott and John H. Burton, did not show a reduction to practice before Dr. Finney's date of invention. Because the Board imposed an overly strict requirement for testing to show reduction to practice, this court reverses and remands.

BACKGROUND

This interference involves Dr. Finney's United States Patent No. 4,791,917, which was accorded the benefit of its May 15, 1980 parent application, and the Scott and Burton application, Serial No. 07/241,826, which was accorded the benefit of its parent application Serial No. 06/264,202, filed May 15, 1981. Although the Scott and Burton application claims a joint invention of both applicants, Dr. Scott is the sole inventor of the subject matter in interference No. 102,429.

The invention is a penile implant for men unable to obtain or maintain an erection. The prosthetic device is a self-contained unit that permits the patient to simulate an erection. The implant contains two reservoirs connected through a valve. The invention operates by shifting the inflating liquid between the two reservoirs. When the penis is flaccid, the invention maintains inflating liquid in a reservoir at the base of the penis. A simulated erection occurs when the liquid shifts through the valve into the elongated reservoir implanted in the forward section of the penis.

Prior art devices fell into two categories: flexible rods and inflatable devices. Flexible rods had the disadvantage of making the penis permanently erect. The prior inflatable devices relied on fluid from a source and pump external to the body to inflate tubes ***1060** implanted in the penis. These devices also had several disadvantages.

The Interference Count at issue states:

> An implantable penile prosthesis for implanting completely within a patient's penis comprising at least one elongated member having a flexible distal forward section for implantation within the pendulous penis, said forward section being constructed to rigidize upon being filled with pressuring fluid; a proximal, rearward section adapted to be implanted within the root end of the penis, said rearward section containing a fluid reservoir chamber, externally operable pump means in said member for transferring fluid under pressure to said flexible distal forward section of said member for achieving an erection; and valve means positioned within said member which open when said pump is operated so that fluid is forced from said pump through said valve means into said flexible distal forward section of said chamber.

The parties to this interference had contested related subject matter in an earlier interference, No. 101,149. The count of 101,149 was a species of the generic count in this interference. Dr. Scott won that earlier interference.

In this interference, No. 102,429, Dr. Finney's application has an earlier filing date than Scott's application. Dr. Scott still has, however, an earlier conception date. Dr. Scott did not present evidence of diligence after conception of his invention. *See, e.g., Griffith v. Kanamaru*, 816 F.2d 624, 626, 2 USPQ2d 1361, 1362 (Fed.Cir.1987). Rather, Dr. Scott opted to show an actual reduction to practice before Dr. Finney's date of invention.

Before the Board, Dr. Scott's primary evidence of actual reduction to practice was a videotape. The videotape showed an operation where the surgeon inserted Dr. Scott's prototype device into the penis of an anesthetized patient. The videotape showed the surgeon manipulating the implanted device. Several times the device simulated an erection when the

surgeon manipulated the valve. Several times the fluid filled the forward reservoir. Several times the surgeon returned the penis to a flaccid condition by draining the fluid back into the rear reservoir. The Board found:

> It is uncontested that the penile implant used in the in-and-out procedure did rigidify the penis by pressurization of the rear chamber and did produce an erection. After the device was actuated to form the erection, the valve mechanism was manipulated to allow the device to become flaccid....

Board opinion at 8-9.

Although not part of the count, the parties agree that the invention envisions implantation of two devices--one on either side of the penis. In the videotaped demonstration, the surgeon implanted only a single prosthesis into the patient. Although using only a single prosthesis, the videotape showed a penis with enough rigidity to produce an erection. After manipulating the implanted device through the skin to simulate having and losing an erection, the surgeon removed Dr. Scott's prototype and inserted a prior art external pump mechanism.

Dr. Scott supplied other evidence as well. He presented evidence of testing for leakage, disclosed that the fabrication material was common in implanted devices, and supplied the testimony of Dr. Drogo K. Montague, an expert in the field. Dr. Montague personally handled the device at issue and viewed the videotape. He testified that the video showed, even with only a single tube, sufficient rigidity for intercourse.

In opposition, Dr. Finney testified personally about the difficulty of determining sufficient rigidity for intercourse on the basis of insertion in an anesthetized patient. Both Drs. Finney and Montague agreed that insertion of two tubes would greatly enhance rigidity.

The Board discerned insufficient evidence to show reduction to practice. Specifically, the Board determined that Dr. Scott had not shown utility, i.e., that the device would successfully operate under actual use conditions for a reasonable length of time. Thus, the Board required "testing of an implantable medical device under actual use conditions or testing under conditions that closely simulate ***1061** actual use conditions for an appropriate period of time." Board opinion at 8.

Because Dr. Scott had not tested his device in actual intercourse or in similar conditions to intercourse for a proper period of time, the Board determined that Dr. Scott had not reduced his invention to practice. The Board awarded the count to Dr. Finney. This appeal followed.

## DISCUSSION

[1][2] The issue of reduction to practice is a question of law which this court reviews *de novo*. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376, 231 USPQ 81, 87 (Fed.Cir.1986), *cert. denied*, 480 U.S. 947, 107 S.Ct. 1606, 94 L.Ed.2d 792 (1987). This court reviews the Board's factual findings under the clearly erroneous standard. *Coleman v. Dines*, 754 F.2d 353, 356, 224 USPQ 857, 859 (Fed.Cir.1985).

[3] The Scott and Burton application was copending with that of Dr. Finney. Consequently, as the junior party in this interference, Dr. Scott had the burden to show prior invention by a preponderance of evidence. *Bosies v. Benedict*, 27 F.3d 539, 542, 30 USPQ2d 1862, 1864 (Fed.Cir.1994); *Harding v. Steingiser*, 318 F.2d 748, 748, 138 USPQ 32, 33 (CCPA 1963). To show prior invention, the junior party must show reduction to practice of the invention before the senior party, or, if the junior party reduced to practice later, conception before the senior party followed by reasonable diligence in reducing it to practice. *See Griffith*, 816 F.2d at 626.

[4] To show reduction to practice, the junior party must demonstrate that the invention is "suitable for its intended purpose." *Steinberg v. Seitz*, 517 F.2d 1359, 1363, 186 USPQ 209, 212 (CCPA 1975) (quoting *In re Dardick*, 496 F.2d 1234, 1238, 181 USPQ 834, 837 (CCPA 1974)). When testing is necessary to show proof of actual reduction to practice, the embodiment relied upon as evidence of priority must actually work for its intended purpose. *Newkirk v. Lulejian*, 825 F.2d 1581, 1582, 3 USPQ2d 1793, 1794 (Fed.Cir.1987). Because Dr. Scott relied on such testing, this court must examine the quality and quantity of testing asserted to show a reduction to practice.

Testing sufficient to show a reduction to practice has often been at issue in interference proceedings. *Newkirk*, 825 F.2d at 1582 ("proof of actual reduction to practice requires demonstration that the embodiment relied upon as evidence of priority actually worked for its intended purpose"); *see also Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1445, 223 USPQ 603, 607 (Fed.Cir.1984)

(same); *Wiesner v. Weigert*, 666 F.2d 582, 588, 212 USPQ 721, 726 (CCPA 1981) (same). By the same token, this court has also indicated "that '[s]ome devices are so simple and their purpose and efficacy so obvious that their complete construction is sufficient to demonstrate workability.' " *King Instrument Corp. v. Otari Corp.*, 767 F.2d 853, 861, 226 USPQ 402, 407 (Fed.Cir.1985), *cert. denied*, 475 U.S. 1016, 106 S.Ct. 1197, 89 L.Ed.2d 312 (1986) (quoting *Eastern Rotorcraft Corp. v. United States*, 384 F.2d 429, 431, 155 USPQ 729, 730 (Ct.Cl.1967)). Indeed, the Supreme Court, in a case featuring evidence of testing, cited approvingly three decisions of the United States Court of Appeals for the District of Columbia which stated that simple devices need no testing to show reduction to practice. *See Corona Cord Tire Co. v. Dovan Chem. Corp.*, 276 U.S. 358, 383, 48 S.Ct. 380, 387-88, 72 L.Ed. 610 (1928) (citing *Roe v. Hanson*, 19 App.D.C. 559 (1902); *Lindemeyr v. Hoffman*, 18 App.D.C. 1 (1901); and *Mason v. Hepburn*, 13 App.D.C. 86 (1898).

[5][6][7] In cases requiring testing, this court's predecessor addressed many times the nature of testing necessary to show reduction to practice. Several important principles emerge from these cases. For instance, the testing requirement depends on the particular facts of each case, with the court guided by a common sense approach in weighing the sufficiency of the testing. *Gellert v. Wanberg*, 495 F.2d 779, 783, 181 USPQ 648, 652 (CCPA 1974); *Gordon v. Hubbard*, 347 F.2d 1001, 1006, 146 USPQ 303, 307 (CCPA 1965). Reduction to practice does not require "that the invention, when tested, be in a commercially satisfactory stage of development." *Dardick*, 496 F.2d at 1238; ***1062** *Steinberg*, 517 F.2d at 1363; *Goodrich v. Harmsen*, 442 F.2d 377, 383, 169 USPQ 553, 559 (CCPA 1971). Testing need not show utility beyond a possibility of failure, but only utility beyond a probability of failure. *Taylor v. Swingle*, 136 F.2d 914, 917, 58 USPQ 468, 471 (CCPA 1943). When reviewing the sufficiency of evidence of reduction to practice, this court applies a reasonableness standard. *Holmwood v. Sugavanam*, 948 F.2d 1236, 1238, 20 USPQ2d 1712, 1714 (Fed.Cir.1991).

Complex inventions and problems in some cases require laboratory tests that "accurately duplicate actual working conditions in practical use." *Elmore v. Schmitt*, 278 F.2d 510, 513, 125 USPQ 653, 656 (CCPA 1960); *accord Koval v. Bodenschatz*, 463 F.2d 442, 447, 174 USPQ 451, 455 (CCPA 1972) (testing of electrical circuit breaker did not test higher voltages); *Anderson v. Scinta*, 372 F.2d 523, 527, 152 USPQ 584, 587 (CCPA 1967) (testing of windshield wiper blades did not simulate effect of wind on windshield); *but cf. Paivinen v. Sands*, 339 F.2d 217, 225-26, 144 USPQ 1, 8-9 (CCPA 1964) (oscilloscope testing of magnetic switching circuit necessarily involved high speed switching). In *Elmore*, the Court of Customs and Patent Appeals noted that the various tests on a binary counter for sophisticated radar and video equipment did not account for "the resistance and character of load, nature of pulses, including voltage, duration and amplitude, and amount of capacitance used." *Elmore*, 278 F.2d at 512. The court also noted that the tests did not "reproduce[ ] the conditions of temperature, vibration, or sustained operation which would usually be encountered in a specific use." *Id.* *Elmore* demanded closer correlation between testing conditions and actual use conditions because the presence of many variables in that precision electronics field would otherwise raise doubts about the invention's actual capacity to solve the problem.

Less complex inventions and problems do not demand such stringent testing. *See, e.g., Sachs v. Wadsworth*, 48 F.2d 928, 929, 9 USPQ 252, 254 (CCPA 1931), and cases cited in *Corona Cord*, 276 U.S. at 383, 48 S.Ct. at 387- 88. In *Sellner v. Solloway*, 267 F.2d 321, 122 USPQ 16 (CCPA 1959), for example, the inventor presented his invention, an exercise chair, at a birthday party. Because "the device involved and manner in which it is intended to operate are comparatively simple," *id.* at 323, the court sustained the sufficiency of this rudimentary testing by individuals without particular skills.

[8] This court's predecessor well summarized many of these principles:

> A certain amount of "common sense" must be applied in determining the extent of testing required. Depending on its nature, the invention may be tested under actual conditions of use, or may be tested under "bench" or laboratory conditions which fully duplicate each and every condition of actual use, or in some cases, may be tested under laboratory conditions which do not duplicate all of the conditions of actual use. In instances where the invention is sufficiently simple, mere construction or synthesis of the subject matter may be sufficient to show that it will operate satisfactorily.

*Gordon*, 347 F.2d at 1006. This statement captures the underlying principle that governs the nature of testing necessary to show reduction to practice--the

character of the testing varies with the character of the invention and the problem it solves. *See* Sydeman v. Thoma, 32 App.D.C. 362 (1909).

Another predecessor to this court summarized, "the inquiry is not what kind of test was conducted, but whether the test conducted showed that the invention would work as intended in its contemplated use." Eastern Rotorcraft Corp. v. United States, 384 F.2d 429, 431, 155 USPQ 729, 730 (Ct.Cl.1967). Thus, the Court of Claims focused on the workability of the invention in the context of the problem it solved. The nature and complexity of the problem necessarily influence the nature and sufficiency of the testing necessary to show a reduction to practice. In any event, the testing should demonstrate "*the soundness of the principles of operation* of the invention." Wolter v. Belicka, 409 F.2d 255, 263, 161 USPQ 335, 341 (CCPA 1969) (Rich, J., dissenting). The inventor need show only that the invention is "suitable" for its intended use. ***1063**Steinberg, 517 F.2d at 1363 (quoting Dardick, 496 F.2d at 1238).

All cases deciding the sufficiency of testing to show reduction to practice share a common theme. In each case, the court examined the record to discern whether the testing in fact demonstrated a solution to the problem intended to be solved by the invention. *See, e.g.,* Farrand Optical Co. v. United States, 325 F.2d 328, 333, 139 USPQ 249, 253 (2d Cir.1963) ("The essential inquiry here is whether the *advance in the art* represented by the invention ... was embodied in a workable device that demonstrated that it could do what it was claimed to be capable of doing.") (emphasis added). In tests showing the invention's solution of a problem, the courts have not required commercial perfection nor absolute replication of the circumstances of the invention's ultimate use. Rather, they have instead adopted a common sense assessment. This common sense approach prescribes more scrupulous testing under circumstances approaching actual use conditions when the problem includes many uncertainties. On the other hand, when the problem to be solved does not present myriad variables, common sense similarly permits little or no testing to show the soundness of the principles of operation of the invention.

[9] In the prosthetic implants field, polyurethane materials and inflatable penile prostheses were old in the art. They were tested extensively. Only the insertion and hydraulics of a manipulable valve separating two implanted reservoirs were new. Thus, Dr. Scott had the burden to show that his novel valve and dual reservoir system would simulate an erection for sexual intercourse when manipulated through the skin. Consequently, the problem presented to Dr. Scott, when viewed from the vantage point of earlier proven aspects of penile implant technology, was relatively uncomplicated.

In the videotape presentation, Dr. Scott demonstrated sufficiently the workability of his invention to solve the problems of a wholly internal penile implant. The videotaped operation showed both rigidity for intercourse and operability of the valve to inflate and deflate the device through the skin. The use of materials previously shown to work in prosthetic implants over a reasonable period of time also showed the durability of the invention for its intended purpose. In sum, Dr. Scott showed sufficient testing to establish a reasonable expectation that his invention would work under normal conditions for its intended purpose, beyond a probability of failure.

The Board erred by setting the reduction to practice standard too high. The Board erroneously suggested that a showing of reduction to practice requires human testing in actual use circumstances for a period of time. *See* Engelhardt v. Judd, 369 F.2d 408, 410-11, 151 USPQ 732, 734 (CCPA 1966) (human testing of antihistamine and antiserotonin unnecessary in light of tests on laboratory animals). Reduction to practice, however, does not require actual use, but only a reasonable showing that the invention will work to overcome the problem it addresses. The videotape showed the rigidity and manipulability of the valve through the skin necessary for actual use. Experts testified to the invention's suitability for actual use. In the context of this art and this problem, Dr. Scott made that reasonable showing.

The Board rejected these proofs because the device was not actually used during intercourse. In this instance of a solution to a relatively simple problem, the Board required more testing than necessary to show that the device would work for its intended purpose. Even accepting the Board's conclusion that the intended purpose is to facilitate normal sexual intercourse, prior art prosthetic devices had fully tested the workability of most features of Dr. Scott's invention. Dr. Scott used the same tested and workable materials and designs of prior art implants. Only the hydraulics of a fully self-contained internal prosthesis remained to be tested for workability. Dr. Scott adequately showed the workability of these features.

Testing for the full safety and effectiveness of a

prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings. *Cf. In re Sichert*, 566 F.2d 1154, 1160, 196 USPQ 209, 214 (CCPA 1977) (rejecting lack ***1064** of safety challenge to utility of claimed drug); *In re Anthony*, 414 F.2d 1383, 1395, 162 USPQ 594, 604 (CCPA 1969) ("Congress has given the responsibility to the FDA, not to the [PTO], to determine ... whether drugs are sufficiently safe....") (citation omitted); *In re Watson*, 517 F.2d 465, 476, 186 USPQ 11, 19 (CCPA 1975) (same).

The Board's holding that Dr. Scott did not reduce his invention to practice before the May 15, 1980 filing date of Dr. Finney is reversed. Dr. Finney asserted that Dr. Scott abandoned, suppressed, or concealed the invention embodied by the count within the meaning of 35 U.S.C. § 102(g) (1988). The Board did not reach this issue in light of its holding that no reduction to practice occurred. Because the Board has not considered this issue, this court remands for a determination of whether Dr. Scott abandoned, suppressed, or concealed the invention within the meaning of 35 U.S.C. § 102(g).

COSTS

Each party to bear its own costs.

REVERSED AND REMANDED.

34 F.3d 1058, 32 U.S.P.Q.2d 1115

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